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European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2016 Update

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Key Words

Antenatal steroids · Continuous positive airway pressure · Evidence-based practice · Hyaline membrane disease · Mechanical ventilation · Nutrition · Oxygen supplementation · Patent ductus arteriosus · Preterm infant · Respiratory distress syndrome · Surfactant therapy · Thermoregulation

These updated guidelines contain new evidence from recent Cochrane reviews and the medical literature since 2013. Strength of evidence supporting recommendations has been evaluated using the GRADE system. The prenatal care section has been expanded and updated by Prof. Gerard H.A. Visser. There are also new recommendations covering less invasive surfactant administration.

Abstract

Advances in the management of respiratory distress syndrome (RDS) ensure that clinicians must continue to revise current practice. We report the third update of the European Guidelines for the Management of RDS by a European panel of expert neonatologists including input from an expert perinatal obstetrician based on available literature up to the beginning of 2016. Optimizing the outcome for babies with RDS includes consideration of when to use antenatal steroids, and good obstetric practice includes methods of predicting the risk of preterm delivery and also consideration of whether transfer to a perinatal centre is necessary and safe. Methods for optimal delivery room management have become more evidence based, and protocols for lung protection, including initiation of continuous positive airway pres-

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sure and titration of oxygen, should be implemented from soon after birth. Surfactant replacement therapy is a crucial part of the management of RDS, and newer protocols for surfactant administration are aimed at avoiding exposure to mechanical ventilation, and there is more evidence of differences among various surfactants in clinical use. Newer methods of maintaining babies on non-invasive respiratory support have been developed and offer potential for greater comfort and less chronic lung disease. As technology for delivering mechanical ventilation improves, the risk of causing lung injury should decrease although minimizing the time spent on mechanical ventilation using caffeine and if necessary postnatal steroids are also important considerations. Protocols for optimizing the general care of infants with RDS are also essential with good temperature control, careful fluid and nutritional management, maintenance of perfusion and judicious use of antibiotics all being important determinants of best outcome.

Introduction

Respiratory distress syndrome (RDS) remains a significant problem for preterm babies although its management has evolved gradually over the years, resulting in improved survival for the smallest infants but with possible increasing rates of bronchopulmonary dysplasia (BPD) at least in part due to the reduced use of postnatal steroids [1]. Since 2006, a group of neonatologists from various European countries have met on a 3-yearly basis to review the most up-to-date literature and to agree on consensus recommendations for the optimal management of preterm babies with, or at risk of, RDS in order to try and achieve the best outcomes for neonates in Europe. The European Consensus Guidelines for the Management of RDS were first published in 2007, have been updated in 2010 and 2013 and are endorsed by the European Association of Perinatal Medicine [2–4]. The guidelines have been translated into several languages, including Chinese, and although primarily intended for use in Europe, they contain recommendations that can potentially be used anywhere, provided clinicians have access to resources needed to fulfil the standards present in modern neonatal intensive care units (NICU).

Although primarily a disorder of surfactant deficiency resulting in pulmonary insufficiency from soon after birth, the classical pattern of RDS has changed as treatments have evolved over the years. Classical RDS radiographic appearances of 'ground glass with air bronchograms' are rarely seen today due to early surfactant therapy and early continuous positive airway pressure (CPAP). Definitions based on blood gas analysis and inspired oxygen concentrations are also increasingly redundant as clinicians have moved towards a more pragmatic approach of giving surfactant therapy based on clinical assessment of work of breathing and inspired oxygen requirement very early in the clinical course of the disease. Knowing how many babies have genuine RDS is therefore difficult. Of the 4,142 babies from Europe for whom data were submitted to the Vermont Oxford Network during 2015, RDS was coded for about 80% of babies born at 28 weeks' gestation, increasing to 95% at 24 weeks' gestation [5]. However, recent large clinical trials show that when given early CPAP, babies of 26–29 weeks' gestation can be managed without intubation or surfactant about 50% of the time, and the high reported incidence may reflect practice where babies are being coded as having RDS because they were treated with prophylactic or early surfactant.

The aim of the management of RDS is to provide interventions that maximize survival whilst minimizing potential adverse effects, including the risk of BPD. Many strategies and therapies for prevention and treatment of RDS are still being tested in clinical trials, and many new studies are incorporated into updated systematic reviews. These guidelines update the previous three guidelines after critical examination of the most up-to-date evidence available in early 2016. We have employed a similar format of summarizing the relevant issues requiring consideration followed by evidence-based recommendations supported by a score using the GRADE system to reflect the authors' views on the strength of evidence supporting each of the recommendations [6]. Quality of evidence and strength of recommendations are summarized in table 1.

Prenatal Care

There are no generally effective means to improve the outcome of infants by preventing the common causes of either spontaneous or elective preterm births. However, in pregnant women at risk of spontaneous preterm birth, due either to previous preterm birth or where a short cervix has been identified on ultrasound examination, use of progesterone has been associated with clinical benefits to the infant including reduced preterm delivery rates and reduced perinatal mortality [7]. However, the findings may not be generally applicable to all modes of adminis-

Table 1. Representations of quality of evidence and strength of recommendations

Quality of evidence	
High quality	A
Moderate quality	B
Low quality	C
Very low quality	D
Strength of recommendation	
Strong recommendation for using intervention	1
Weak recommendation for using intervention	2

tration [8], and there are no data to suggest a longer-term benefit (or harm) on infant and childhood outcomes [9]. Cervical cerclage may also reduce preterm birth in at-risk pregnancies, but it is not clear whether it improves perinatal outcome [10]. Adequate spacing between pregnancies may reduce the risk of recurrent preterm delivery; a Caesarean delivery is likely to increase the risk of spontaneous preterm delivery in a subsequent pregnancy.

Interventions to prevent RDS and improve outcome can also begin before birth even if delivery cannot be prevented. There is often warning of impending preterm delivery, and interventions can be considered that might prolong gestation or reduce the risk of an adverse outcome by 'preparing' the fetus, or enabling transfer to a centre with more experience of dealing with problems of prematurity. Cervical length measurement, in combination with fetal fibronectin testing, can help to determine which women are at low risk of delivery within 7 days, and perhaps allow a more judicious use of antenatal treatments [11]. Extremely preterm babies at risk of RDS should be born in centres where appropriate skills are available, as long-term health outcomes are better if they receive their initial neonatal care in tertiary units [12]. In cases of prenatal prelabour rupture of membranes, antibiotics can delay preterm delivery and reduce neonatal morbidity including the need for surfactant, although co-amoxiclav should be avoided because of an association with an increased risk of necrotizing enterocolitis (NEC) [13]. Magnesium sulphate given to women with imminent preterm delivery marginally reduces the incidence of cerebral palsy [14], although a more recent longer-term follow-up of an Australian cohort showed no differences by school age [15]. Tocolytic drugs can be used in the short term to delay birth and allow safe transfer to a perinatal centre or to enable prenatal corticosteroids time to take effect. However, no beneficial effects of tocolytic drugs have been shown in randomized controlled trials (RCTs) in which corticosteroids were given in both arms of the trial [16]. Given their limited value, only drugs that are safe for the mother should be considered, i.e. oxytocin antagonists or Ca channel blockers [17]. Both drugs have similar efficacy and perinatal outcome; the former has the fewest maternal side effects.

Prenatal corticosteroids given to mothers with anticipated preterm delivery improve survival, reduce the risk of RDS, NEC and intraventricular haemorrhage, and a single course does not appear to be associated with any significant maternal or short-term fetal adverse effects. The beneficial effects of antenatal steroids were similar in studies conducted in the 1970s as in those conducted more recently implying that they remain beneficial in the presence of modern neonatal care [18]. Prenatal corticosteroid therapy is recommended in all pregnancies with threatened preterm labour before 34 weeks' gestation where active care of the newborn is anticipated. Although there are limited RCT data in babies <26 weeks' gestation or very immature twins, observational studies support the concept that antenatal corticosteroids also reduce mortality in these infants [19, 20]. In pregnancies between 34 and 36 weeks' gestation, prenatal steroids will also reduce the risk of short-term respiratory morbidity but not mortality, and there is a paucity of data on longer-term follow-up [21]. When given before elective Caesarean section (CS) at 37–39 weeks, they reduce the risk of admission to the NICU, although the number needed to treat is >20 [22]. Follow-up data on term babies exposed to antenatal steroids are limited.

The optimal treatment to delivery interval is more than 24 h and less than 7 days after the start of steroid treatment; beyond 14 days the benefits are diminished. There is a continuing debate as to whether steroids should be repeated 1 or 2 weeks after the first course for women with threatened preterm labour. Such repeat courses do not reduce the risk of neonatal death, but reduce RDS and other short-term health problems, although birth weight is reduced and long-term beneficial effects are lacking [23]. The WHO recommends that a single repeat course of steroids may be considered if preterm birth does not occur within 7 days after the initial course and subsequent assessment demonstrates that there is a high risk of preterm birth in the next 7 days [24]. It is unlikely that repeat courses given after 32 weeks' gestation improve outcome, and recent long-term follow-up studies show no benefit by school age in terms of reduction in death or disability if repeat courses are used [25].

A recent RCT from low- to medium-income countries showed a higher neonatal mortality and maternal infec-

tion rate in women given prenatal steroids [26]. The majority of babies were >2 kg at birth, and these data emphasize the importance of adequate dating of duration of pregnancy, assessment of risk of preterm birth and availability of neonatal facilities before considering antenatal steroids. Steroids are potent drugs with many potential side effects. When given appropriately they improve outcome. If not, then side effects, such as impaired fetal and placental growth, apoptosis in the brain and increased infection risks, may prevail. Use of steroids should be reduced by adequate preterm birth risk assessment and by avoidance of early elective CS. In some cases when an early CS is needed, establishment of fetal lung maturity may be better than giving steroids to all women [27]. In addition, there is no evidence that delivering preterm infants by CS rather than allowing vaginal delivery improves outcome.

Recommendations

1 Mothers at high risk of preterm birth <28–30 weeks' gestation should be transferred to perinatal centres with experience in the management of RDS (C1).
2 Clinicians should offer a single course of prenatal corticosteroids to all women at risk of preterm delivery, from when pregnancy is considered potentially viable up to 34 completed weeks' gestation (A1).
3 A single repeat course of antenatal steroids may be appropriate if the first course was administered more than 1–2 weeks previously and the duration of pregnancy is <32–34 weeks' gestation when another obstetric indication arises (A2).
4 Antenatal steroids can also be considered for CS not in labour up to 39 weeks (B2). However, there should be a clear medical reason to do an early CS, and elective CS should not be performed <39 weeks' gestation.
5 In late preterm pregnancy at risk of early birth, a course of antenatal steroids may also be considered provided there is no evidence of chorio-amnionitis (C2).
6 In women with symptoms of preterm labour, cervical length and fibronectin measurements should be considered to prevent unnecessary hospitalization and use of tocolytic drugs and/or antenatal steroids (B2).
7 Clinicians should consider short-term use of tocolytic drugs in very preterm pregnancies to allow completion of a course of prenatal corticosteroids and/or in utero transfer to a perinatal centre (B1).

Delivery Room Stabilization

Babies with RDS have difficulty maintaining alveolar aeration after birth, although most try to breathe for themselves, and therefore any support of transition is 'stabilization' rather than 'resuscitation'. Updated European Resuscitation Guidelines were published in 2015, highlighting recent evidence-based approaches to assessing and supporting babies during the immediate postnatal period, including newborn life support where required [28]. Resuscitation training courses tend to focus on babies with terminal apnoea secondary to prolonged hypoxia with appropriate emphasis of achieving lung inflation by observing adequate chest lift, and judging a baby to be well when they are pink. When dealing with preterm babies with RDS, we must train ourselves to think differently, allowing the infant to pass gradually through transition if possible whilst exposing them to a minimum number of interventions that may cause harm [29].

Timing of clamping of the umbilical cord is important. Traditionally the cords of preterm infants were clamped and cut immediately after birth to enable the paediatricians to begin resuscitation as quickly as possible under a radiant heater. Studies in cannulated fetal lambs showed that cord clamping before lung aeration has occurred results in acute transient reduction in left ventricular output. Delaying clamping until the lungs are aerated and left atrial blood flow is established results in smoother transition with no fluctuation in blood pressure [30]. Randomized trials show that promoting placentofetal transfusion results in a higher haematocrit, transiently higher blood pressure with less need for inotropic support and fewer intraventricular haemorrhages [31]. Umbilical cord milking in preterm babies may be an alternative to delayed cord clamping, particularly at CS or in emergency situations but concerns about safety remain, and there is a paucity of long-term follow-up data for either method [32, 33]. Our previous strong recommendation in support of delaying cord clamping has been criticized, as evidence on which it was based had relatively few extremely preterm babies and a paucity of longer-term follow-up data [34]. A recent trial of 208 singleton fetuses <32 weeks' gestation showed no difference in hospital outcomes, but improved neurodevelopmental outcome at 18 months [35]. The Australian Placental Transfusion Study will compare outcomes in 1,600 babies <30 weeks' gestation randomized to immediate or cord clamping delayed for 60 s and will hopefully provide a more definitive answer [36]. After birth the baby should be placed in a clear polyethylene bag and under a radiant warmer to maintain body temperature (see later).

Stabilization of preterm babies with RDS may require inflation of the lung with blended air/oxygen, and how this should be done has been studied in some detail. Air is better than oxygen for resuscitation of term babies in terms of reduced mortality, and 100% oxygen is also probably harmful to preterm babies, causing increased

oxidative stress [37]. Protocols to achieve normal transitional saturations measured by pulse oximetry at the right wrist usually result in extremely low-birth-weight infants requiring around 30–40% oxygen by about 10 min of age [38, 39]. Starting low and working up is better than starting high and working down in terms of reducing oxidative stress, although starting with 21% may be too low for the most immature babies who may need at least 30% oxygen, and further studies are under way to resolve this issue [40]. Measuring heart rate by auscultation or cord palpation may not be accurate, and although ECG in the delivery room offers a more rapid practical alternative to pulse oximetry for measuring heart rate, it is not widely available and may not offer any meaningful advantage in terms of improving outcome. The need to provide effective measurable CPAP from birth makes the T piece device a better choice than a self-inflating anaesthetic bag [41]. Routine suctioning is not needed before CPAP is applied [42]. CPAP during stabilization can be delivered either by face mask or a short nasal prong [43]. For spontaneously breathing preterm babies, provision of CPAP alone is optimal, and routine use of positive pressure breaths should be discouraged because of the risk of lung injury [44]. Gentle positive pressure ventilation should be provided for babies who remain apnoeic or bradycardic, and there is no apparent advantage of a sustained inflation over intermittent positive pressure breaths [45]. The Sustained Aeration of Infant's Lungs trial has been launched and will hopefully more fully resolve this issue. Only a minority of babies should require intubation for stabilization. If intubation is required, the correct placement of the endotracheal tube can be quickly verified clinically by auscultation and using a colorimetric CO_2 detection device before administering surfactant which can be done prior to radiographic confirmation of RDS in most circumstances.

Recommendations

1 If possible delay clamping the umbilical cord for at least 60 s to promote placentofetal transfusion (B1). Cord milking is a reasonable alternative if delayed cord clamping is not possible (B2).
2 Oxygen for resuscitation should be controlled using a blender. An initial concentration of 30% oxygen is appropriate for babies <28 weeks' gestation, and 21–30% for those of 28–31 weeks, and adjustments up or down should be guided by pulse oximetry from birth (B2).
3 In spontaneously breathing babies, stabilize with CPAP of at least 6 cm H_2O via mask or nasal prongs (A1). Gentle positive pressure lung inflations using about 20–25 cm H_2O peak inspiratory pressure should be used for persistently apnoeic or bradycardic infants (B1).
4 Intubation should be reserved for babies who have not responded to positive pressure ventilation via face mask (A1). Babies who require intubation for stabilization should be given surfactant (B1).
5 Plastic bags or occlusive wrapping under radiant warmers should be used during stabilization in the delivery suite for babies <28 weeks' gestation to reduce the risk of hypothermia (A1).

Surfactant Therapy

Surfactant therapy plays an important role in the management of babies with RDS. By 2013 it was accepted that surfactant *prophylaxis*, in the current era of prenatal steroid use, was no longer indicated for babies receiving stabilization using non-invasive respiratory support, and a strategy of initiation of CPAP from birth with *early selective surfactant administration* for babies showing signs of RDS was recommended, with the caveat that if the baby *needed* intubation for stabilization, surfactant should be given [4, 46]. The overall aim was to avoid mechanical ventilation (MV) where possible, or to reduce its duration, whilst administering surfactant as early as possible in the course of RDS if it was deemed necessary. To this end the INSURE (intubate-surfactant-extubate to CPAP) technique was recommended with suggested protocols for surfactant administration when babies showed signs of RDS and needed more than 30% inspired oxygen to maintain saturations in the normal range. Since the 2013 guideline update there have been further studies aimed at optimizing surfactant use, by avoiding potential exposure to lung injury using less invasive methods of administration, and avoiding positive pressure ventilation through an endotracheal tube.

Surfactant Administration Methods

Surfactant administration is a skill that requires an experienced clinical team comfortable with neonatal intubation and MV if needed. Until recently the vast majority of clinical trials of surfactant used bolus administration via an endotracheal tube with a short period of manual ventilation or MV to distribute the drug followed either by continued MV or immediate (or early) extubation to CPAP when spontaneous breathing had resumed if the INSURE method was used. INSURE was recommended in the 2013 guideline on the basis that it reduced lung injury [47]; however, in the original studies sedation for intubation was considered optional, and this was an area for debate. Since then there have been studies to determine if surfactant administration without endotracheal intuba-

Table 2. Surfactant preparations (animal-derived) licensed in Europe in 2016

Generic name	Trade name	Source	Manufacturer	Dose (volume)
Beractant	Survanta®	Bovine	Ross Laboratories (USA)	100 mg/kg/dose (4 ml/kg)
Bovactant	Alveofact®	Bovine	Lyomark (Germany)	50 mg/kg/dose (1.2 ml/kg)
Poractant alfa	Curosurf®	Porcine	Chiesi Farmaceutici (Italy)	100–200 mg/kg/dose (1.25–2.5 ml/kg)

tion results in improved outcomes, on the basis that avoidance of *any* positive pressure ventilation may be beneficial. Two similar methods of administering surfactant via a fine catheter without 'traditional' intubation have been studied. The first, developed in Germany and now used widely in parts of Europe, uses a fine flexible catheter positioned in the trachea whilst the baby is kept on CPAP, using laryngoscopy and Magill's forceps [48], also known as LISA (less invasive surfactant administration). The second, developed in Australia, uses a more rigid thin vascular catheter that is stiff enough to be positioned in the trachea under direct laryngoscopy without forceps whilst the baby is kept on CPAP [49], also known as MIST (minimally invasive surfactant treatment). With both methods the aim is to maintain spontaneous breathing on CPAP whilst surfactant is gradually administered over several minutes using a syringe without resorting to routine bagging. Both of these methods have been compared to traditional intubation for surfactant administration followed by MV. Large cohort studies from the German neonatal network with experience of this method were encouraging, reporting reduced use of MV and less BPD [50]. A randomized non-blinded clinical trial of extremely preterm infants between 23 and 27 weeks' gestation showed no significant increase in survival without BPD in those treated with LISA although these infants required less ventilation, had fewer pneumothoraces and a reduction in severe intraventricular haemorrhage. However, nearly 75% of the intervention group eventually needed MV, and the rate of desaturations was significantly higher in this group [51]. Although direct comparison with INSURE reported improved outcomes in one study [52], reanalysis of the data could not reproduce statistical significance when included in a meta-analysis, and therefore to date this is still uncertain [53]. Nebulization to deliver surfactant has not yet reached a stage where it can be recommended for routine clinical use [54].

Surfactant Preparations

Surfactants currently available in Europe are shown in table 2. Animal-derived (formerly called natural) surfactants are better than older synthetic (protein-free) preparations, containing only phospholipids, at reducing pulmonary air leaks and mortality [55]. Lucinactant is a synthetic surfactant that contains sinapultide, a protein analogue mimicking surfactant protein-B (SP-B) activity. It works better than the protein-free synthetic surfactants, but is not yet proven to be better than animal-derived surfactants and is not available in Europe [56]. Synthetic surfactants containing both SP-B and SP-C analogues are also currently under evaluation in clinical trials [57]. Comparisons among animal-derived surfactants have also shown differences in clinical effect. Overall there is a survival advantage when a 200 mg/kg dose of poractant alfa is compared with 100 mg/kg of beractant or 100 mg/kg poractant alfa to treat RDS but it is unclear whether this is a dose effect or related to differences in the surfactant preparations [58].

When to Treat with Surfactant?

Where possible babies at risk of RDS should be started on CPAP from birth, and where possible maintained on CPAP without resorting to intubation. If RDS develops, and surfactant is needed, the earlier in the course of the disease surfactant is given, the better the outcome, in terms of reducing air leaks [59], or maximizing the chance of successful avoidance of MV if the INSURE technique is used [60]. However, prophylactic INSURE does not confer any advantage over initiation of CPAP alone [61]. The previous guideline recommendation was that surfactant should be administered when FiO_2 >0.30 for very immature babies and >0.40 for more mature infants, based on thresholds used in trials comparing earlier versus later surfactant from an era when CPAP was not in widespread use. Recent observational studies have confirmed that FiO_2 >0.30 by 2 h of age on CPAP is predictive of CPAP failure by 6 h of age, and that those who fail CPAP have a poorer outcome [62]. This strengthens the argument for interventions that reduce CPAP failure, such as early surfactant given by minimally invasive methods, to avoid lung injury. Methods to measure the presence or absence of endogenous surfactant, such as lamellar body count in

gastric aspirate, may help in deciding whom to treat [63]. However, methods that require laboratory expertise around the clock are unlikely to be widely adopted and a simple bedside test that can be used within the NICU is needed.

There may be a need for further doses of surfactant. Randomized trials in the era before non-invasive ventilation was used widely showed that multiple doses reduced the risk of air leaks [64] but this may not be true in the era of early CPAP. Using a larger dose of 200 mg/kg poractant alfa for the first dose will reduce the need for redosing [58]. Multiple INSURE has also been successfully employed and does not appear to worsen outcomes [65]. Predicting who is likely to fail INSURE using clinical criteria and blood gases may help define a population that would be reasonable to maintain on MV [66].

Recommendations

1 Babies with RDS should be given a *natural* surfactant preparation (A1).
2 A policy of early rescue surfactant should be standard (A1) but there are occasions when surfactant should be administered in the delivery suite, such as those who require intubation for stabilization (B1).
3 Babies with RDS should be given rescue surfactant early in the course of the disease. A suggested protocol would be to treat babies ≤26 weeks' gestation when FiO_2 requirements >0.30 and babies >26 weeks' when FiO_2 requirements >0.40 (B2).
4 Poractant alfa in an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or beractant for rescue therapy (A1).
5 INSURE should be considered for infants who are failing on CPAP (A2).
6 LISA or MIST may be used as alternatives to INSURE for spontaneously breathing infants (B2).
7 A second and sometimes a third dose of surfactant should be administered if there is evidence of ongoing RDS such as persistent oxygen requirement and need for MV (A1).

Oxygen Supplementation beyond Stabilization

For the last decade there has been an enormous effort to determine optimal saturation targets for preterm infants, addressing the balance between avoiding negative effects of excess oxygen exposure such as retinopathy of prematurity (ROP) and potential negative effects of prolonged low-grade hypoxia such as increased mortality, NEC or adverse neurodevelopmental outcome. The NeOProM collaboration was established to enable the results of 5 large-scale randomized clinical trials with similar study design from different parts of the world to be used in a prospective meta-analysis to give greater power to detect relatively small but important differences in outcomes such as mortality [67]. Each trial was designed to assess effects of saturation targeting in a lower range (85–89%) compared to a higher range (91–95%) with blinding provided by oximeters which were offset to read higher or lower than the actual saturation within the target range. The SUPPORT trial from the USA, the first to be completed, showed the low saturation target group had a halving of ROP in survivors, but a worrying 4% increase in mortality [68]. An interim meta-analysis combining these data and all accrued at that time from the UK and Australian BOOST-II trials was undertaken at the request of the data safety-monitoring committee. This confirmed the excess mortality when targeting lower saturations, and further enrolment was stopped in the UK and Australia/New Zealand [69]. In the meantime the Canadian COT trial was published reporting no significant differences in death or significant neurodisability, nor any significant difference in ROP rates [70]. The outcomes from a combined analysis of the UK and Australia/New Zealand BOOST-II trials have recently been published showing increased mortality in the low-saturation target group [71]. Meta-analysis of all available data in 2014 has further added to uncertainty around ideal saturation targets. Combining the data from 5 studies showed no difference in death or disability at 24 months, no difference in mortality at 24 months but an increase in mortality before hospital discharge in the restricted oxygen group [72]. Rates of ROP were similar in the two groups, although there was an excess of NEC in the lower saturation group [72]. In 2016 the most up-to-date NeOProM meta-analysis confirmed that the lower target range (85–89%) was associated with a significant increased risk of death but there was no difference between the 2 target ranges in terms of disability at 18–24 months [73]. Also, the lower target range did not reduce BPD or severe visual impairment but it did increase the risk of NEC requiring surgery or causing death [73]. Current best evidence suggests that it is reasonable to recommend aiming for saturations between 90 and 94% rather than lower, although there is still a high level of uncertainty where ideal saturation targets lie.

The ability to maintain saturations within the predefined target may also be important. There is a tension between narrower alarm limits, which increase alarm frequency, nurse fatigue and potential wider fluctuations in saturation and wider limits which may expose infants to potentially longer periods of time outside the desired range [74]. Even in the best units many babies spend

much time outside the target range, more usually hyperoxic than hypoxic [75, 76]. Secondary analysis of data from the COT trial oximeters showed an association of prolonged episodes of hypoxaemia (saturation <80% for >1 min) with later death or adverse neurodevelopmental outcome [77]. Servo-controlled oxygen delivery algorithms show promise in terms of maintaining babies within the target range for proportionately more time; however, to date no studies have been done to see if this can improve outcome [78].

Recommendations

1 In preterm babies receiving oxygen, the saturation target should be between 90 and 94% (B2).
2 To achieve this, suggested alarm limits should be 89 and 95% (D2).

Non-Invasive Respiratory Support

Non-invasive respiratory support is considered the optimal method of providing assistance to preterm babies with breathing problems and includes CPAP, various types of ventilation provided through soft nasal prongs or masks which are collectively called nasal intermittent positive pressure ventilation (NIPPV) and humidified oxygen delivered by high-flow nasal cannulae (HF). They are used where possible as a substitute for MV as they are less injurious to the lung. Traditionally non-invasive methods were used as a step-down from MV through an endotracheal tube, and initially CPAP was the main method employed, with early randomized trials showing reduction in need for re-intubation if CPAP was used instead of head box oxygen [79]. More recently it has been shown that initiation of CPAP from birth rather than routine intubation for stabilization or prophylactic surfactant treatment is better at preventing lung injury, although it is important to try to determine when CPAP alone is not going to be effective [80]. CPAP devices provide a flow of gas under controlled pressure delivered to the nose via interfaces that are applied tightly to the face to create a seal. Distending pressure has several theoretical benefits including splinting the upper airway, maintaining lung expansion and preventing end-expiratory alveolar collapse, thereby facilitating endogenous surfactant release [81]. There seem to be no differences among devices used to deliver CPAP pressure, although the interface may be important [82]. In the delivery room a short pharyngeal tube is a reasonable alternative to face mask CPAP to free up hands during early stabilization [43]. In the NICU short binasal prongs are better than single prongs although one small study suggested that nasal masks may be the most effective interface for ensuring CPAP success [83]. All these interfaces have to be applied tightly to the face and carry a risk of facial distortion and nasal trauma.

Bilevel CPAP is another variant of CPAP, or low-pressure NIPPV, that uses small pressure differences between inspiratory and expiratory phases. These are typically delivered through CPAP flow driver devices and generate low peak inspiratory pressures of about 9–11 cm H_2O which can be synchronized using an abdominal pressure transducer. It is unclear whether these equate to changes in tidal volume or simply an overall increase in the CPAP level. Although increasingly popular, there is not much evidence that it confers any significant advantage over CPAP [84, 85].

NIPPV is also used as first- or second-line respiratory support in many units, with conventional ventilators used to deliver peak inspiratory pressures similar to those on MV, with or without synchronization, but through nasal prongs [86]. NIPPV reduces extubation failure, but has not consistently been beneficial in reducing BPD [87]. Studies where NIPPV was most successful used synchronization of inspiratory pressure delivered through a signal from an abdominal Graseby capsule. These ventilators are not widely available and delivering effective synchronization using flow sensors is challenging due to large leaks during CPAP, and it is unclear whether non-synchronized NIPPV is effective [86, 87]. The NIPPV trial was a large international multicentre randomized trial powered to study the outcome of BPD in 1,009 babies <1,000 g birth weight without specifying the mode of delivering NIPPV, and it showed no difference between babies randomized to NIPPV compared with CPAP [88]. Planned secondary analysis of data from the NIPPV trial also shows no difference in rates of BPD or death when comparing those who received NIPPV compared to bilevel CPAP [89]. Further work is needed to determine the best method of delivering NIPPV and the population most likely to benefit.

Since the 2013 guideline, the use of heated humidified HF as an alternative to CPAP has increased in popularity. A recent meta-analysis of 15 studies comparing HF with other modes of non-invasive respiratory support is reassuring, showing equivalent rates of treatment failure for babies coming off MV and similar rates of BPD, although there is still a relative paucity of data for the extremely preterm population, and wide confidence intervals and heterogeneity in relation to equivalence for 'treatment failure' [90]. A potential mechanism of benefit may be

carbon dioxide washout of the nasopharyngeal space; however, with higher flow rates there is also an element of unquantified additional CPAP. Flow rates of 4.0–8.0 l/min are typically used, with weaning of flow rate determined clinically by FiO_2 levels remaining low and judgement of work of breathing. HF is also being studied as a primary mode of respiratory support in the delivery room [91], and the results of large trials comparing HF with CPAP are awaited [92].

Recommendations

1 CPAP should be started from birth in all babies at risk of RDS, such as those <30 weeks' gestation who do not need intubation for stabilization (A1).
2 The system delivering CPAP is of little importance; however, the interface should be short binasal prongs or a mask, and a starting pressure of about 6–8 cm H_2O should be applied (A2). CPAP pressure can then be individualized depending on clinical condition, oxygenation and perfusion (D2).
3 CPAP with early rescue surfactant should be considered the optimal management for babies with RDS (A1).
4 Synchronized NIPPV, if delivered through a ventilator rather than a bilevel CPAP device, can reduce extubation failure, but may not confer long-term advantages such as reduction in BPD (B2).
5 HF may be used as an alternative to CPAP for some babies during the weaning phase (B2).

Mechanical Ventilation Strategies

Despite best intentions to manage preterm babies on non-invasive respiratory support to protect their lungs, about half of extremely preterm babies with RDS will fail and need support with MV through an endotracheal tube [93]. The aim of MV is to provide 'acceptable' blood gas exchange whilst minimizing the risk of lung injury, hypocarbia and circulatory disturbance. The principle of MV is to recruit atelectatic lung by inflation and optimize lung volume for an even distribution of tidal volumes at pressures set to prevent atelectasis and overinflation with minimal oxygen requirement. Overinflation increases the risk of air leaks such as pneumothorax and pulmonary interstitial emphysema. However, ventilation at too low a pressure risks areas of lung becoming repeatedly atelectatic during expiration, which can generate inflammation. Modern neonatal ventilators offer various modes, with pressure-limited ventilation (PLV) and volume-targeted ventilation (VTV) being the most common. Although pressure-limited modes are relatively simple to manage and allow ventilation even during the presence of a large endotracheal tube leak, tidal volumes may increase dangerously during rapid improvement of lung compliance after lung fluid clearance or surfactant administration. Excessively high tidal volumes injure the lung and lead to hypocarbia which can subsequently cause brain injury such as periventricular leukomalacia or intraventricular haemorrhage [94, 95]. In contrast, inadequately low tidal volumes, which can occur after a decrease in lung compliance, cause uneven distribution of tidal volumes, increase work of breathing, agitation of the infant and hypercarbia. VTV enables clinicians to ventilate with less variable tidal volumes and real-time weaning of pressure as lung compliance improves. There are different ways of VTV regulation, such as inspiratory pressure, flow or time adjustment, but better tidal volume stability is a final result of all these ventilator-driven algorithms. VTV compared to PLV may reduce BPD or death and intraventricular haemorrhage, and shorten duration of MV [96, 97]. Both an initial set tidal volume of about 5 ml/kg in VTV and an estimated peak inspiratory pressure according to observation of chest movement in PLV may need to be adjusted according to the baby's own respiratory efforts and gas exchange assessment. The required tidal volume may need to increase with increasing postnatal age if the baby remains ventilated [98]. An 'open lung' is achieved by setting adequate PEEP, and this must be adjusted according to lung biophysical properties [99]. To determine optimum PEEP on conventional ventilation, each incremental change of PEEP should be evaluated by responses in FiO_2 and CO_2 levels. Lung compliance is very dynamic during the management of RDS, particularly following surfactant therapy, and for an individual baby rapid ventilator responses may be needed.

When high pressures are needed to achieve adequate lung inflation, high-frequency oscillatory ventilation (HFOV) may be a reasonable alternative to MV. HFOV allows gas exchange with very low tidal volumes delivered at very fast rates in lungs held open at optimal inflation by a continuous distending pressure. The optimum continuous distending pressure on HFOV is about 1–2 cm H_2O above the closing pressure identified by deterioration of oxygenation during stepwise reductions in airway pressure after full lung recruitment [100]. A recently updated meta-analysis of RCTs comparing HFOV with conventional PLV shows a small inconsistent reduction in BPD in the HFOV group; however, this benefit is counteracted by increased air leaks in those on HFOV [101]. Although most trials reporting neurodevelopmental outcome have not identified any differences, a recent long-term pulmonary follow-up of one RCT demonstrated better small airway function at 11–14 years of age in infants originally managed with HFOV [102]. Whatever

mode is accepted as standard within an individual unit, it is important that all staff should be familiar with its use.

Overdistension should be considered if a baby is deteriorating on MV following surfactant administration, or when an increase in mean airway pressure is followed by increasing oxygen requirement. During ventilation hypocarbia and severe hypercarbia should be avoided because of their association with an increased risk of BPD, periventricular leukomalacia and intraventricular haemorrhage, and methods of continuous CO_2 assessment can be helpful during initiation of ventilation. When satisfactory gas exchange is achieved and spontaneous breathing is present, weaning of ventilation should be started immediately. The VTV mode enables automatic weaning by a decrease in peak inspiratory pressure *in real time* as compliance improves. Some babies will only require ventilation for a very short period of time. Babies with RDS improve rapidly following surfactant therapy and can be quickly weaned to low ventilator settings with a view to an early trial of extubation to CPAP. Early extubation of even the smallest babies is encouraged, provided it is judged clinically safe and they have acceptable blood gases on low ventilator settings [103]. Extubation may be successful from 7–8 cm H_2O mean arterial pressure on conventional modes and from 8–9 cm H_2O continuous distending pressure on HFOV. Keeping stable very preterm babies on low-rate MV for longer periods does not improve the chance of successful extubation [104]. Extubating to a relatively higher level of CPAP pressure of 7–9 cm H_2O will improve the chance of successfully remaining off the ventilator [105].

Several strategies have been used specifically to improve the success of non-invasive ventilation and shorten the duration of MV including caffeine therapy, permissive hypercarbia and postnatal steroid treatment.

Caffeine Therapy

Since the 2010 guideline, caffeine therapy has been recommended as an essential part of newborn respiratory care [3]. The Caffeine for Apnea of Prematurity (CAP) study showed that caffeine facilitated earlier extubation with a significant reduction in BPD, and follow-up at 18 months showed a reduction in neurodisability [106, 107]. Caffeine was strongly recommended for babies with RDS coming off ventilation and also for babies on non-invasive support to reduce risk of apnoea, although this was less evidence based, as the CAP trial had relatively few infants who were treated prophylactically. Recently there have been several large cohort studies supporting the use of earlier rather than later caffeine in terms of improving outcomes such as BPD [108–110]. Although this relationship cannot be assumed to be cause and effect, it seems reasonable in the absence of randomized trials and good evidence of safety to recommend caffeine routinely as part of a strategy to minimize the need for MV. The standard dose of caffeine citrate is 20 mg/kg loading and 5–10 mg/kg daily maintenance. Some studies suggest that doubling these doses may further reduce the risk of extubation failure, although tachycardia is more frequent [111, 112].

Permissive Hypercarbia

In the 2013 guideline moderate hypercarbia was considered tolerable during weaning from MV provided pH was acceptable (above 7.22) in order to reduce time spent on MV [113]. More recently post hoc analysis of data from the SUPPORT trial shows an association between higher $PaCO_2$ and risk of death, intraventricular haemorrhage, BPD and adverse neurodevelopmental outcome, again highlighting the need for further evaluation of ideal $PaCO_2$ targets [95]. The PHELBI trial randomized ventilated preterm babies <29 weeks' gestation and <1,000 g birth weight to two target $PaCO_2$ levels for the first 14 days of ventilation, the higher arm reaching about 10 kPa and the lower about 8 kPa [114]. The study was stopped early and analysis performed on 359 of a planned 1,534 infants. There was no difference in the primary outcome of death or BPD, with trends to worse outcomes in the higher target group, including an increase in NEC in the smallest babies and more death or BPD in infants with initial severe lung disease in the higher target group. Tolerating moderate hypercarbia to the level of the lower target group of the PHELBI trial seems reasonable.

Postnatal Steroids

One of the key objectives of RDS management is to improve survival whilst preventing BPD, and although management of BPD is beyond the remit of this guideline, it is worth considering strategies that can reduce lung inflammation during the acute stage of RDS and potentially limit the time on MV. Postnatal dexamethasone reduces BPD but its use declined dramatically when it was associated with an increased risk of cerebral palsy [115]. However, BPD is also associated with adverse neurological outcome and the higher the risk of BPD, the more potential benefit there will be from a course of postnatal steroids [116]. Low-dose dexamethasone (<0.2 mg/kg day) is currently recommended for babies who remain ventilator dependent after 1–2 weeks [117], and work is ongoing to determine if even lower doses are effective [118]. Low-

dose hydrocortisone also has the potential to reduce BPD, but again long-term follow-up data are needed before this therapy can be routinely recommended [119]. Inhaled budesonide seems an obvious logical alternative to systemic steroids and recently a large RCT confirmed that prophylactic inhaled budesonide reduces both persistent ductus arteriosus (PDA) and BPD [120]. There was a trend toward increased mortality with treatment, and long-term developmental follow-up is not yet available. The addition of budesonide to natural surfactant preparations may also decrease lung inflammation in ventilated preterm babies and reduce the risk of BPD, although this will need further verification by randomized multicentre trials [121].

Recommendations

1 After stabilization, MV should be used in babies with RDS when other methods of respiratory support have failed (A1). Duration of MV should be minimized (B2).
2 Targeted tidal volume ventilation should be employed as this shortens the duration of ventilation and reduces BPD and intraventricular haemorrhage (A1).
3 Avoid hypocarbia (A1) as well as severe hypercarbia (C2) as these are associated with an increased risk of brain injury. When weaning from MV, it is reasonable to tolerate a modest degree of hypercarbia, provided the pH remains above 7.22 (B2).
4 Caffeine should be used to facilitate weaning from MV (A1). Early caffeine should be considered for all babies at high risk of needing MV, such as those <1,250 g birth weight, who are managed on non-invasive respiratory support (C1).
5 A short tapering course of low-dose dexamethasone should be considered to facilitate extubation in babies who remain on MV after 1–2 weeks (A2).
6 Inhaled steroids cannot be recommended for routine use to reduce BPD until further safety data become available.

Monitoring and Supportive Care

To achieve best outcomes for preterm babies with RDS they should have optimal supportive care, with monitoring physiological variables and appropriate responses. The ability to maintain body temperature from birth is extremely important. Pulse oximetry and possibly ECG monitoring from birth provide rapid information of responses to stabilization [122]. In the NICU there should be access to continuous pulse oximetry, ECG monitoring as well as monitoring Pa_{CO_2} levels. Detection of exhaled CO_2 can ensure correct placement of endotracheal tubes, and continuous measurement of end-tidal CO_2 also gives useful information showing trends in gas exchange. Umbilical or radial arterial cannulation is indicated if it is anticipated there will be need for regular blood gas analyses. Transcutaneous oxygen and CO_2 monitoring has also been used to access continuous information for trending but can cause skin injury [123]. Methods of monitoring cerebral oxygenation are also available with potential to guide clinicians about optimal cerebral blood flow but no clear clinical benefit has yet been identified [124]. Access to laboratory support is necessary to enable close monitoring of serum electrolytes and haematological values ideally using microsampling techniques. Blood pressure should be recorded via indwelling arterial lines or intermittently using approved oscillometric devices. Around-the-clock access to radiology services and portable ultrasound is also essential as these are often used to confirm RDS diagnosis, exclude air leaks and confirm correct placement of endotracheal tubes and central lines.

Temperature Control

Maintaining normal body temperature during stabilization and after admission is important for babies with RDS. The most recent International Liaison Committee on Resuscitation guidelines for resuscitation recommend maintaining body temperature between 36.5 and 37.5°C, and suggest that to do this effectively in preterm babies requires environmental temperature in the delivery room to be above 25°C [28]. Initial stabilization should be performed with the baby wrapped in a polyethylene bag under a radiant warmer [125]. Addition of an exothermic mattress may increase the risk of overheating [126]. Warming and humidification of gases used for stabilization may also improve temperature [127]. Following stabilization infants should be nursed in incubators with high relative humidity to reduce insensible water losses. Servo-controlled incubators with skin temperature set at 36.5°C decrease neonatal mortality [128]. For the smallest babies humidity of 60–80% should be used initially and reduced as skin integrity improves, as maintaining high humidity may promote bacterial or fungal growth. WHO guidelines promote the use of kangaroo mother care in stable low-birth-weight babies as a means of maintaining temperature and reducing mortality in lower income settings, and increasingly kangaroo mother care is being used to maintain temperature to maximize maternal-infant bonding, even in babies on MV [129, 130].

Recommendation

1 Maintain core temperature between 36.5 and 37.5°C at all times (C1).

Early Fluids and Nutritional Support

During transition after birth, fluid management is challenging. The smallest infants have very high initial transcutaneous losses of water, and water and sodium move from the interstitial to the intravascular compartments. Typically fluids are initiated at about 70–80 ml/kg/day and adjustments individualized according to fluid balance, weight change and serum electrolyte levels. A modest early postnatal weight loss is normal. Regimens with more restricted compared with more liberal fluids have better outcomes, with reductions in PDA, NEC and BPD [131]. Delaying introduction of sodium supplementation until beyond the third day or 5% weight loss will also improve outcome [132]. Nutrition should be started immediately after stabilization. Enteral feeding volumes will initially be limited, so parenteral nutrition should be used. Early initiation of amino acids results in positive nitrogen balance [133], reduced time to regain birth weight and enhanced weight gain at discharge [134]. Higher phosphorus and potassium intakes may be needed in cases of enhanced amino acid supply [135]. Parenteral lipids should also be started from day 1 [136]. For stable infants a small amount (0.5–1 ml/kg/h) of breast milk can be started early to promote maturation of the intestinal tract [137]. There is no evidence of increased NEC with early initiation of feeds or advancing feeds more rapidly up to 30 ml/kg/day in stable very low-birthweight babies [138, 139]. Mother's milk is the preferred option for initiation of feeding; however, if not available then pasteurized donor breast milk is better than formula as it reduces the risk of NEC [140].

Recommendations

1 Most babies should be started on intravenous fluids of 70–80 ml/kg/day while being kept in a humidified incubator although some very immature babies may need more (B2). Fluids must be tailored individually according to serum sodium levels and weight loss (D1).
2 Sodium intake should be restricted over the first few days of life and initiated after onset of diuresis with careful monitoring of fluid balance and electrolyte levels (B1).
3 Parenteral nutrition should be started from birth. Protein can be started at 2–2.5 g/kg/day from day 1 (B2). Lipids should also be started from day 1 and quickly built up to 3.0 g/kg/day as tolerated (C2).
4 Enteral feeding with mother's milk should be started from the first day if the baby is haemodynamically stable (B1).

Antibiotics

It had been considered good practice to screen babies who present with early respiratory distress for infection; however, it is now known that routine antibiotic prophylaxis has the potential to do more harm than good [141–143]. Guidelines usually offer advice on when to screen for sepsis based on additional risk factors such as maternal chorio-amnionitis or early signs of septicaemia in the hope that antibiotics are only prescribed for those at greatest risk [144]. If screening for sepsis is necessary, then antibiotics should be started empirically whilst waiting for test results, such as negative blood cultures at 36–48 h and negative serial C-reactive protein measurements, before stopping them. At present it is reasonable not to use routine antibiotics in preterm babies with RDS at low risk such as planned delivery by elective CS. For those who have been started empirically on antibiotics, the shortest possible course should be used.

Recommendation

1 Antibiotics are often started in babies with RDS until sepsis has been ruled out, but policies should be in place to narrow the spectrum and minimize unnecessary exposure. A common regimen includes penicillin or ampicillin in combination with an aminoglycoside (D2). Antibiotics should be stopped as soon as possible once sepsis has been excluded (C1).

Managing Blood Pressure and Perfusion

Hypotension and low systemic blood flow are associated with adverse long-term outcome, although the two are not always closely correlated [145]. Blood pressure is lower with decreasing gestation and increases gradually over the first 24 h of life, but varies widely at each gestational age [146]. Defining hypotension as a mean arterial pressure less than gestational age in weeks is widely accepted; however, many babies with RDS will breach this threshold and there is no evidence that treating 'numerically defined' hypotension will influence outcome [147]. Functional echocardiography can be used to assess cardiac output and look for evidence of poor systemic blood flow to help decide whether treatment is needed, although this skill is not available in many units [148]. Hypotension during RDS may be related to hypovolaemia, large left-to-right ductus or atrial shunts, or to myocardial dysfunction, and confirmation of low systemic blood flow and its cause may help to guide appropriate treatment. Hypovolaemia is probably overdiagnosed and can be minimized by delaying cord clamping. Dopamine is more effective than dobutamine at increasing blood pressure and can improve cerebral blood flow in hypotensive infants [149], although dobutamine may be a more rational choice during the transitional period due

Table 3. Summary of recommendations

Prenatal care	– Preterm babies at risk of RDS should be born in centres where appropriate care, including MV, is available – Judicious antenatal assessment should include risk of preterm delivery and need for maternal corticosteroids if the risk is moderate or high. Tocolytics can be used to allow time for steroids to take effect or for safe transfer where appropriate
Delivery room stabilization	– Aim to delay cord clamping at birth by at least 1 min, or cut the cord long and milk towards the baby after birth – Stabilize the baby in a plastic bag under a radiant warmer to prevent heat loss – Gently support breathing using CPAP if possible, and, if inflations are needed, avoid excessive tidal volumes. ECG and pulse oximetry can help guide heart rate response to stabilization. Start with about 21–30% oxygen and titrate up or down as needed – Intubation at birth should be considered only for those not responding to the above, although early intubation and surfactant may be required for babies who demonstrate early signs of severe RDS such as chest retractions and high oxygen requirements
Respiratory support and surfactant	– An animal-derived (natural) surfactant should be used and given as early as possible in the course of RDS. For very immature infants, a treatment threshold of FiO_2 0.30–0.40 on CPAP seems reasonable. Repeat doses of surfactant may be required if there is ongoing evidence of RDS – Babies can often be extubated to CPAP or NIPPV immediately following surfactant, and judgement needs to be made if an individual baby will tolerate this. Consider minimally invasive surfactant (LISA or MIST) as an alternative to INSURE if your unit has appropriate expertise – For those who require MV, aim to ventilate for as short a time as possible, avoiding hyperoxia, hypocarbia and volutrauma. This may be best achieved with VTV and saturation alarm limits set at 89 and 95% – Caffeine therapy should be used routinely to minimize the need for ventilation. Babies should be maintained on non-invasive respiratory support in preference to MV if possible. Beyond 1–2 weeks, steroids should be considered to facilitate extubation if the baby remains ventilated – In preterm babies receiving oxygen, the saturation target should be between 90 and 94%. To achieve this, suggested alarm limits should be 89 and 95%
Supportive care	– Maintain body temperature at 36.5–37.5° C at all times – Start parenteral nutrition immediately with amino acids and lipids with initial fluid volumes about 70–80 ml/kg/day for most babies and restrict sodium during the early transitional period – Enteral feeding with mothers' milk should also be started on day 1 if the baby is stable – Antibiotics should be used judiciously and stopped early when sepsis is ruled out – Blood pressure should be monitored regularly, aiming to maintain normal tissue perfusion, if necessary using inotropes. Hb should be maintained at acceptable levels – Protocols should be in place for monitoring pain and discomfort and consideration given for non-pharmacological methods of minimizing procedural pain and judicious use of opiates for more invasive procedures

to its ability to increase contractility and decrease afterload [150]. Studies assessing different thresholds for intervention with dopamine to determine if inotrope therapy influences long-term outcome are ongoing [151]. Epinephrine and hydrocortisone can be used in refractory hypotension when dopamine and dobutamine have failed although there is little new evidence on safety or efficacy [152, 153].

Maintaining a reasonable haemoglobin (Hb) concentration is also important. Randomized trials comparing targeting more restrictive versus more liberal Hb concentrations (about 1–2 g/dl lower) result in less need for blood transfusion without affecting hospital outcomes, and suggested Hb thresholds for transfusion are based on these slightly more restrictive values [154]. However, long-term follow-up has shown some better cognitive outcomes in those with more liberal Hb thresholds [155], and further trials are ongoing to resolve this issue [156].

PDA may provide clinical problems for very preterm babies with RDS in terms of low blood pressure, poor tissue perfusion, pulmonary oedema and difficulty weaning from MV. As all infants start life with an open ductus arteriosus, it is difficult to make recommendations for when to treat it. Surgical ligation of PDA is associated with worse long-term neurodevelopmental outcome, and although it is not clear whether this is due to the PDA or its treatment, surgery should only be considered after medical therapy has failed [157]. Permissive tolerance of PDA

is an acceptable strategy provided the infant is thriving, tolerating feeds and on minimal respiratory support [158]. Cyclo-oxygenase inhibitors such as indomethacin or ibuprofen promote ductal closure, although ibuprofen has fewer side effects [159]. More recently paracetamol has been shown to promote ductal closure although more trials with long-term follow-up are needed before it can be routinely recommended [160]. Early echocardiography-guided therapy of large PDAs is being studied as a means of improving outcomes whilst minimizing exposure to treatment [161, 162].

Recommendations

1 Treatment of hypotension is recommended when it is confirmed by evidence of poor tissue perfusion such as oliguria, acidosis and poor capillary return rather than purely on numerical values (C2).
2 Hb concentration should be maintained within normal limits. A suggested Hb threshold for babies on respiratory support is 11.5 g/dl (haematocrit 35%) in week 1, 10 g/dl (haematocrit 30%) in week 2 and 8.5 g/dl (haematocrit 25%) beyond 2 weeks of age (C2).
3 If a decision is made to attempt therapeutic closure of the PDA, then indomethacin or ibuprofen have been shown to be equally efficacious: ibuprofen should be used as there is less transient renal failure or NEC (A2).

Pain and Sedation

Newborn babies can experience pain, and during management of RDS it is important to consider the comfort of the baby. Procedures such as venepuncture, intubation and MV all have potential to cause discomfort, and it is good practice to have mechanisms for evaluating pain using validated scoring systems [163]. Many clinicians prefer to use a combination of a short-acting opiate, muscle relaxant and atropine to maximize comfort and improve the chances of successful intubation [164]. However, there is a balance between ensuring comfort during laryngoscopy and not oversedating infants when trying to maintain them on non-invasive respiratory support [165]. Once stable on ventilation there is usually no need for routine sedation [166]. Sucrose analgesia and other non-pharmacological methods may be employed to reduce procedural pain [167].

Recommendations

1 The routine use of morphine ınfusions in ventilated preterm infants is not recommended (C2).
2 Opioids should be used selectively, when indicated by clinical judgement and evaluation of pain indicators (D1).

Miscellaneous

Since the 2010 guidelines we have included a brief section on aspects of RDS management that arise infrequently. Each year new genetic mutations affecting surfactant systems are reported; these are usually fatal, and congenital SP-B and ABCA3 deficiency are beyond the scope of this guideline. Surfactant therapy may also be useful in situations where secondary surfactant inactivation occurs such as meconium aspiration, congenital pneumonia and pulmonary haemorrhage. There are few clinical trials supporting surfactant use in pneumonia [168], although in a recent observational study babies with RDS complicated by pneumonia seemed to require more surfactant [169]. Surfactant therapy improves oxygenation in babies with pulmonary haemorrhage, and although there are no RCTs looking at outcomes compared with no treatment [170], a recent small trial comparing two different natural surfactant preparations in pulmonary haemorrhage showed more rapid improvement in oxygenation with poractant alfa compared with beractant, but with no differences in other outcomes [171]. There are no data to support routine or rescue use of inhaled nitric oxide (iNO) in preterm babies [172]. Despite this, iNO continues to be used in many units, particularly for ill babies with severe respiratory failure and poor oxygenation [173, 174]. There is an argument for rationalizing the use of iNO for specific populations of preterm infants, for example those with premature rupture of membranes or documented pulmonary hypertension and conducting further clinical trials [175, 176]. Until these are completed, iNO cannot be recommended for use in preterm babies.

Recommendations

1 Surfactant can be used for RDS complicated by congenital pneumonia (C1).
2 Surfactant therapy can be used to improve oxygenation following pulmonary haemorrhage (C1).
3 The use of iNO in preterm babies should be limited to those in clinical trials or those with severe hypoxaemia secondary to documented pulmonary hypertension (D2).

Summary of Recommendations

A summary of all recommendations is given in table 3.

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A European panel of experts was convened under the auspices of the European Association of Perinatal Medicine to update evidence-based guidelines on the management of RDS. The guidelines were prepared using evidence-based methods as summarized in table 1. We are grateful to Roger Soll and Eric Shinwell for their helpful comments on the final draft of these guidelines.

Disclosure Statement

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